The importance of being inventive

Critics claim that patents on genes may lead to very broad monopolies and inhibit further innovation. The European patent system provides efficient legal means to address these issues

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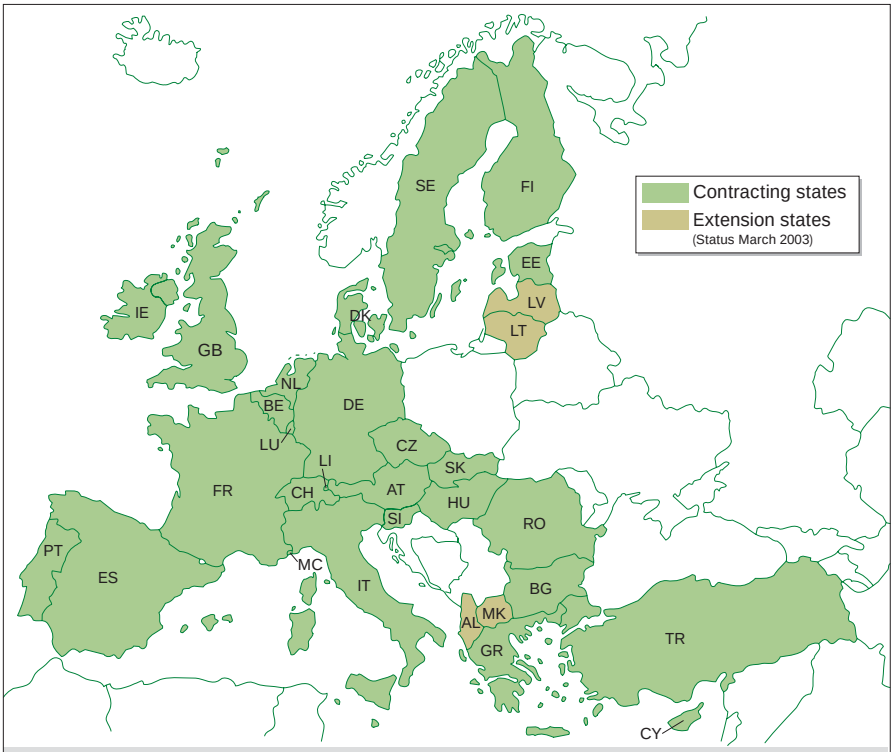
In Summer 2003, the European Commission referred eight EU member states—Germany, Austria, Belgium, France, Italy, Luxembourg, The Netherlands and Sweden—to the European Court of Justice for their failure to implement the European Directive (98/44/EC) on the legal protection of biotechnological inventions (European Commission, 2003). The German government recently published its proposal to implement the Directive, but the German parliament still has to debate and adopt the law in question. There are several reasons for this delay, but the public debate about the patentability of inventions in biotechnology has certainly had an important role. Here we outline the most important legal provisions for the patenting of nucleic acids and polypeptides in Europe and explain how these influence the examination and granting of patents. In addition we discuss the most prominent arguments brought forward in the public debate.

Some legal scholars regard patents as a 'natural' property right that an inventor holds over his invention—comparable to the copyright on literature, music or artwork. More often, patents are seen as a means of promoting research activity by granting the inventor a restricted monopoly in exchange for the complete disclosure of his invention. A patent thus gives the patent owner only the right to exclude others from commercially using—producing, selling or licensing—the patented subject. In many cases additional provisions, such as the approval of pharmaceuticals, have to be fulfilled before the invention can be used commercially. The exclusive right conferred by a patent is restricted in time and is valid only in those countries where the patent was granted. After the expiry of the patent, which is usually 20 years from the date of filing, the invention becomes a public resource, free for everyone to use. Patents therefore provide an incentive for research and development by conferring a limited monopoly on the patent owner. For the pharmaceutical industry this aspect is particularly important, because the investment needed to develop a new medicine is estimated at about €895 million over an average period of 12–13 years (European Federation of Pharmaceutical Industries and Associations, 2003). A patent puts its proprietor in a better position to recoup these costs. Patents also represent a highly valuable source of information because they must be published—in Europe, 18 months after filing—and everything needed for the invention has to be made available, including sequence information, cell lines and bacterial strains (Cook-Deegan & McCormack, 2001).

Patent laws have been constantly refined and adapted to new technologies and developments, but critics claim that the



Contracting states						Extension states	
AT	Austria	ES	Spain	LU	Luxembourg	AL	Albania
BE	Belgium	FI	Finland	MC	Monaco	LT	Lithuania
BG	Bulgaria	FR	France	NL	Netherlands	LV	Latvia
CH	Switzerland	GB	United Kingdom	PT	Portugal	MK	F.Y.R. of Macedonia
CY	Cyprus	GR	Greece	RO	Romania		
CZ	Czech Republic	HU	Hungary	SE	Sweden		
DE	Germany	IE	Ireland	SI	Slovenia		
DK	Denmark	IT	Italy	SK	Slovakia		
EE	Estonia	LI	Liechtenstein	TR	Turkey		

Fig 1 | Member states of the European Patent Organisation

current regulations are not adequate for biological matter, namely genes, polypeptides and living organisms. Aside from ethical objections, they argue that biological matter *per se* cannot be patented because it has always existed in nature and thus does not constitute an invention, but rather a mere discovery. More practically, many biologists, both in academia and industry, fear that broad patents on genes and proteins could prevent further research by other parties, which could have negative consequences for biomedical research and health care.

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In fact, granting a patent does not stop further research. Most national patent laws allow non-commercial research on a patented subject and do not consider this an infringement. Such research exemptions have been instigated to allow the improvement of existing patented technology. The extent of these exemptions can differ from country to country; it is up to national courts to decide what constitutes a patent infringement and what falls under a research exemption.

The European Patent Convention (EPC) (www.european-patent-office.org/legal/epc) allows an inventor to apply for a patent in all its member states (see Fig 1), 27 at present, with a single application, which is examined and eventually decided upon by the European Patent Office (EPO) (www.european-patent-office.org). This examination process is largely public: third parties can inspect files on the Internet and submit observations to the EPO. Parties other than the applicant are free to object to patent claims that they regard as unjustified, and interested persons and institutions—usually competing firms, but individuals and non-commercial institutions as well—can file an opposition within a period of nine months after the EPO has granted a patent. The outcome of such an opposition may be maintenance of the patent in the original or in an amended, often more restricted, form or the complete revocation of the patent. The EPO's decisions can also be appealed against before the Boards of Appeal of the EPO, an independent authority. After being granted, a European Patent is adopted as a national patent in all designated member states of the EPC. As mentioned above, patent infringement can then be prosecuted only by national courts and the same holds true for applications to invalidate a patent after the nine-month opposition period has passed. (See Fig 2 for recent numbers of European patent applications examined, granted or opposed.)

During the 1990s the European Commission drafted a Directive to harmonize the legal system specifically for patents in biotechnology, with the aim of promoting the development of biotechnology in the EU. After ten years of discussion and close consultation with various interest groups, the European Directive on the legal protection of biotechnological inventions (European Commission, 1998) was adopted in 1998 by the Council and the European parliament, and upheld by the European Court of Justice against an appeal by The Netherlands supported by Italy and Norway (European Court of Justice, 2001). It was enacted into the Regulations of the EPC in 1999 by a decision of the Administrative Council of the EPO, representing all EPC member states. In addition to the requirements of the EPC, which apply to all patent applications, Directive 98/44/EC now forms the legal basis for the examination and granting of European patents in the field of biotechnology. The directive has clarified the requirements that inventors have to meet when they seek patent protection for nucleic acids or polypeptides.

Most patent systems in the world are based on three general principles. First, patents should be granted only for technical subject matter. Abstract subjects such as discoveries, pure information, aesthetic creations and mathematical theories are not considered to be patentable. Second, a patentable invention must be novel and a creation that goes beyond previous art (that is, everything published or made publicly available before the filing date). Third, it must be industrially applicable (as defined in Europe and Japan) or have utility (in the USA). (See Fig 3 for a breakdown of patent applications by country.)

The first of these principles is often used as an argument against the patenting of nucleic acids and proteins because these already existed in nature and thus were allegedly only discovered and not invented. Apart from the fact that natural products, such as microbial antibiotics, hormones and plant extracts, have been patented for more than a century, it is also important to realize that nucleic acids or proteins do not usually occur in an isolated form in nature. It requires technology and inventive activity to isolate them and make them technically usable, which often requires considerable investment. The patent system was applied to protect the outcome of such endeavour against copying by others and to promote research and development in this area. Furthermore, the concept of novelty in the patent system is not the same as in common usage. 'Novelty' in patent law is

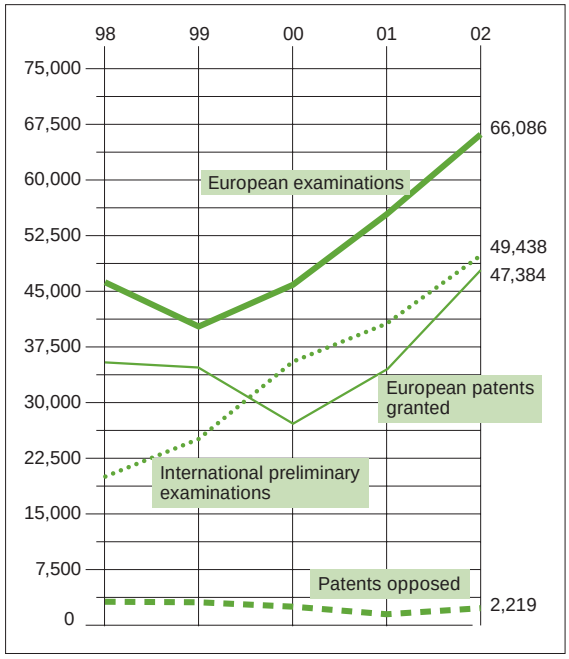

Fig 2 | Completed patent examinations and patent oppositions at the EPO, 1998–2002

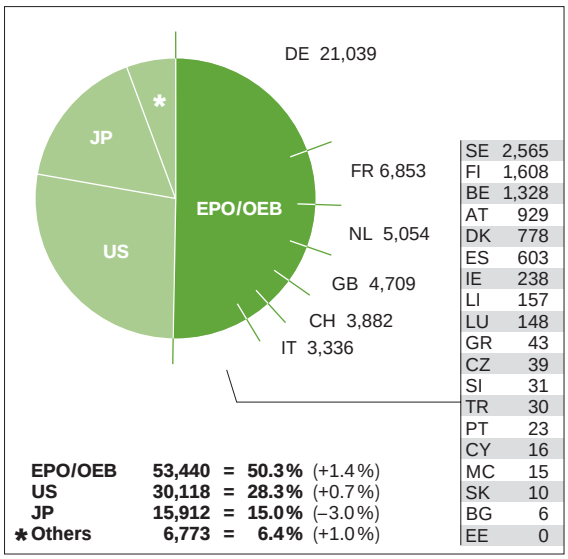

Fig 3 | Patent applications to the EPO: breakdown by applicants' country, residence or place of business

defined as everything that has not been made available to the public by means of written or oral description, by use, or in any other way. For example, when a patent application relating to human H2-relaxin was filed, the protein had not previously been described. Moreover, it was not found existing freely in nature, but had to be isolated to be available to the public. It was therefore regarded as an invention and not a mere discovery (EPO, 1995). Another example of the distinction between a discovery and an invention based on the patent concept of novelty is the isolation of an antibiotic-producing microorganism from soil. Although the bacterium existed in nature, it was not available to the public because it had never been isolated. Furthermore, its existence was not known before the filing of the patent application. The microorganism is therefore regarded as novel. Nevertheless, the mere isolation of a natural substance is not sufficient for patentability: there must in addition be an inventive activity. With regard to genes, the EC Directive explicitly states that "the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions," and that "the industrial application of a sequence or partial sequence must be disclosed in the patent application."

Thus, the EPO, in line with the Directive, requires the applicant to describe the industrial application of a claimed nucleic acid or polypeptide at the time of filing. In practice, this means that the patent examiner has to determine not only whether the invention is novel and inventive but also whether the applicant has described a meaningful technical use for it. At the peak of genomic sequencing, many applications were filed for sequences of unknown function, such as expressed sequence tags (ESTs). In accordance with the Directive, such applications could not lead to a patent, because they lacked a specific indication of industrial application. Broad functional descriptions, such as "useful as a probe for chromosome 21" or "can be employed in a screen for binding partners" are likewise not sufficient because they apply to many other sequences and are thus not specific to the claimed molecule. With the rise of bioinformatics a second group of applications has appeared, in which assumptions about the function of a claimed sequence are made on the basis of its homology to known sequences. In most cases, such applications also do not qualify for a patent because they fail to be sufficiently specific and often lack an inventive step. For example, a patent on a seven-transmembrane receptor without a specific function or ligand was recently revoked after an opposition at the EPO because it lacked industrial application and an inventive step (EPO, 2002a). In another case, the Boards of Appeal of the EPO decided that a human homologue with 80% sequence identity to a known mouse monokine could not be patented: the Boards argued that the isolation of the human homologue could not be considered inventive because it was performed in a straightforward manner with mouse cDNA as a probe. Moreover, the person skilled in the art had an incentive to isolate the human homologue because the potential therapeutic value of human cytokines was known (EPO, 2002b).

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The practice of the EPO to require an industrial application for a claimed biological sequence is in line with the current practice of the two other major patent offices in the world—the US Patent Office and the Japanese Patent Office. The US Patent Office recently adopted new guidelines that raised the bar on the utility and written description requirements for patenting DNA. Furthermore, comparative trilateral studies on the patentability requirements for biotechnological inventions in the USA, Japan and the EPC show a high degree of harmonization between the three big patent offices (EPO, 2002c).

Serious concern has been voiced in some circles that granting patents for genes and nucleic acids could inhibit innovation, lead to unjustified monopolies and block the development of new drugs and diagnostics. Such effects are difficult to assess, although various studies have been made on the economic consequences of biotechnology patents and on the impact of patenting on research activities (Nuffield Council on Bioethics, 2002; Scherer, 2002; Resnik, 2003; Stott & Valentine, 2003; The Royal Society, 2003; Thomas, 2003). Most studies agree that the requirement for an inventive step should ensure that patents are only granted for real inventions and not for the result of routine methods. In Europe, the provisions of the EPC and the decisions of the Boards of Appeal, which adapt the interpretation of the EPC to new developments in technology, constantly update the requirements for the rigorous examination of an inventive step. In addition, the requirement to describe industrial application means that patents are not granted for speculative applications filed for nucleic acids before an actual function or application has been determined.

The scope of a patent claim also reflects the contribution of the invention to the research field. A pioneering invention that opens up a new field of technology is awarded a broader scope of protection than an invention that pertains only to a

small improvement on an existing method. Awarding a broad patent does not as a rule prevent further development and improvement of the original invention. The explosion of biotechnology research in the USA and in Europe, notwithstanding the grant of a large number of patents, speaks for itself. This research has given rise to many more patents based on further work with existing, patented technology. The owner of such a 'dependent' patent has to obtain licences on all previous patents on which his invention is based. This could indeed lead to a blockade if the proprietor of an earlier, broader patent refuses to license his patent (Merz *et al*, 2002). However, if those improvements are commercially interesting, it can be advantageous for the proprietor of the original patent to use this improved technology (OECD, 2002). This situation, which occurs in most technical fields, often leads to cross-licensing agreements or so-called patent pools, an agreement between two or more patent owners to license some of their patents to one another or to third parties. The variety of technical fields that are the subject of patent applications is shown in Fig 4.

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During the examination of a patent application, the requirements of novelty and inventive step often lead to a restriction in the scope of claims, simply because broad patent claims are more likely to overlap with the prior art. If, for example, sequence variants having 50% identity with a given sequence are claimed, it is very likely that the claims would include known homologous sequences from other organisms or known sequences from the same organism. The claim would therefore lack novelty and would have to be restricted to a narrower scope. Furthermore, if the examiner has doubts that the invention can be performed over the whole breadth of the scope of the claim—for instance, with very distant variants of a protein that are unlikely to be biologically active—he can ask the applicant to provide further evidence to support the application.

It is often contended that it is difficult to 'invent around' a broad patent on a naturally occurring gene sequence (Nuffield Council on Bioethics, 2002). With this reasoning—in particular referring to Myriad Pharmaceutical's patent on the *BRCA1* gene (Lecrubier, 2002; Andrews, 2003)—it has been alleged that broad patents on gene sequences might lead to monopolies, with detrimental effects on further research. However, the same argument can also be applied to other technical fields, in particular to pharmacy. Most drugs are based on a limited number of compounds that may be difficult to 'invent around'. Many constraints are imposed on the design of a new medicine. It must interact with specific molecules, must cross several physiological barriers in the body and should have few side effects. Moreover, small endogenous molecules, such as dopamine and oestradiol, were used as medicines long before the advent of biotechnology, and patents were granted on such molecules and their variants. Indeed, pharmaceutical companies have for years been avoiding litigation and costly legal battles by cross-licensing or patent pooling. It seems reasonable to suppose that biotechnology companies will follow their example.

Should the owner of a patent be considered to be abusing his monopoly, the situation can be dealt with by using compulsory licensing. Several countries have enacted laws under which a patent proprietor can be forced to license his patented technology at a reasonable price, for example in a public health emergency (Gold, 2003; Gold *et al*, 2002). The extent of such exceptions to patent protection is limited by international contracts to prevent their abuse.

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The patent system has a long and successful history of coping with new technology, of which biotechnology is only one. The European Directive has harmonized the patenting of biotechnological inventions and reaffirmed the strict requirements of inventive step and industrial application already applied in Europe for patents on nucleic acids and polypeptides. The opposition procedure before the EPO allows third parties to achieve the revocation of invalid patents. In addition, national courts can still invalidate patents after the nine-month opposition period. Research exemptions, cross-licensing and patent pools are additional ways of ensuring the continuous development of patented technology. In cases of perceived abuse, interested parties can consider and call for the compulsory licensing of patented technology.

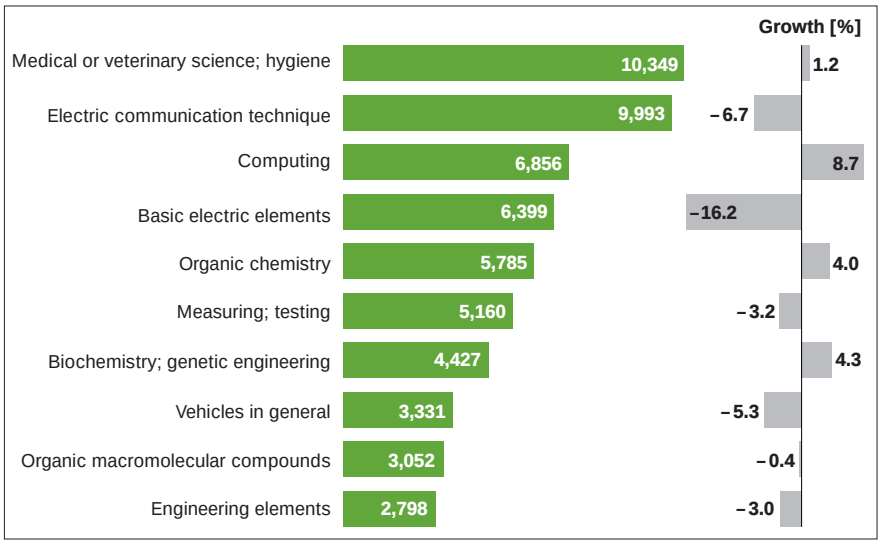

Fig 4 | Top technical fields in applications to the European Patent Office

ACKNOWLEDGEMENTS

The present article is based on personal considerations by the authors and does not necessarily reflect the official position of the European Patent Office on the subject.

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doi:10.1038/sj.embor.7400068